Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-45, 48-65, and 69-80 are pending in the application, with claims 1 and 69 being the independent claims. Claims 1, 2, 5, 6, 27 and 29 are sought to be amended. Support for the amendment to claims 1, 2, 5, and 6 is found, *inter alia*, at paragraphs [207] to [291] of the specification as originally filed. Support for the amendment to claims 27 and 29 is found, *inter alia*, at paragraph [0124] of the specification as originally filed. Claims 46, 47, 66-68, and 81-84 were previously canceled without prejudice. Applicants reserve the right to pursue the canceled subject matter in related applications. Claims 21, 23, 28, 36, 37, 39, 42, 43, 45, 48-58, 63-65, and 69-80 have been withdrawn from consideration by the Examiner as being drawn to non-elected inventions or non-elected species, but remain pending. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Applicants also respectfully remind the Examiner that, in view of the amendments and remarks presented herein, that the present claims "would not have been properly finally rejected on the grounds and art of record in the next Office Action." M.P.E.P. § 706.07(b). Therefore, Applicants respectfully submit that the issuance of a final Office Action after the filing of the present Amendment and Reply and the Request for Continued Examination, filed concurrently herewith, would be improper.

Rejections under 35 U.S.C. § 112, 1st Paragraph

The rejections under the first paragraph of 35 U.S.C. § 112 have been withdrawn. Present Office Action at page 4.

Rejections under 35 U.S.C. § 112, 2nd Paragraph

The rejection of claim 35 and its dependent claims under the second paragraph of 35 U.S.C. § 112, has been withdrawn. Present Office Action at page 4, paragraph 7.B.

Claims 27, 29-35, 38, 40, 41, and 44 remain rejected under the second paragraph of 35 U.S.C. § 112, as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which Applicants regard as their invention. *Id.* at page 4, paragraphs 7.A. and 8. Applicants respectfully traverse this rejection.

With respect to claim 27 and the claims that depend therefrom, the Examiner maintains that there is insufficient antecedent basis for the term "the naturally-occurring genome" in the first line. *Id.* Applicants respectfully disagree with this assertion.

Section 2173.05(e) of the M.P.E.P. provides that:

> Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface.

M.P.E.P. § 2173.05(e) (8th ed., Aug. 2001, Rev. Aug. 2005) (citing *Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359, 60 U.S.P.Q.2d 1216, 1218-19 (fed. Cir. 2001).

Since the phrase, "the naturally-occurring genome," as recited in the claim refers to an inherent component of the vector, (*e.g.*, a eukaryotic virus vector has naturally-occurring type of genome into which a polynucleotide of interest is inserted for

introduction into a host cell), Applicants respectfully maintain that the use of the article "the" is appropriate, and that one of ordinary skill in the art would be able reasonably to ascertain the scope of the claim as written. Nevertheless, solely in an effort to facilitate prosecution, and not in acquiescence to the rejection, claim 27 is amended to recite "...wherein said vector comprises a naturally-occurring type of genome, and wherein said naturally-occurring type of genome of said vector is DNA." Likewise, claim 29 is amended to recite "...wherein the naturally-occurring type of genome of said vector is linear, double-stranded DNA."

Applicants believe that the grounds of rejection of claims 27, 29-35, 38, 40, 41, and 44 under the second paragraph of 35 U.S.C. § 112, have been overcome or otherwise rendered moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

The Rejection of Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61 over Rowlands, Zauderer, and Waterhouse is Traversed

Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands *et al.*, WO 93/01296 (hereinafter "Rowlands"), Zauderer, WO 00/28016 (hereinafter "Zauderer"), and Waterhouse *et al.*, *Nuc. Acids Res. 21*: 2265-66 (1993) (hereinafter "Waterhouse"), as evidenced by Roitt *et al.*, IMMUNOLOGY 67 (6th ed., 2001) (hereinafter "Roitt") and Applicants' specification. (Office Action at Pages 17-18, Section 22.) Applicants respectfully traverse this rejection.

Applicants first note that, in making the rejection under 35 U.S.C. § 103, the Examiner maintains that:

> Rowlands et al. . . .teach a method for producing antibodies in vaccinia infected cells including intracellular antibodies that reads on the presently claimed invention (e.g., see Rowlands et al., abstract; see also paragraph bridging pages 15-16 showing production of "intracellular" antibodies i.e., both heavy and light chains found within the cell and thus said host cells are "capable" of expressing intracellular immunoglobulin molecules; see also page 6, paragraph 3).

Present Office Action at page 6. Applicants respectfully disagree with this characterization of Rowlands.

As set forth in Applicants Reply filed July 21, 2005 (which is incorporated herein by reference), Rowlands does not teach the expression of intracellular immunoglobulin molecules. The passages cited by the Examiner do not describe intracellular immunoglobulin molecules. Rather, these passages indicate only that, whereas Rowlands *et al.* were attempting to express secreted Campath-1H antibodies, there were some light and heavy chains that failed to be secreted into the cell culture medium. The failure of the expressed Campath-1H antibody light and heavy chains to be secreted into the cell culture medium as disclosed in Rowlands does not correlate with the intracellular immunoglobulin molecules of the present invention. The present claims recite that expression of the intracellular immunoglobulin "induces a modified phenotype in a eukaryotic host cell" and that "said modified phenotype is induced via binding of said intracellular immunoglobulin molecule or fragment thereof to an intracellular antigen. There is no showing in Rowlands that antigen-specific intracellular immunoglobulin molecules were formed from the unsecreted Campath-1H light and heavy chains or that

their expression induced a modified phenotype in a eukaryotic host cell by binding an intracellular antigen, as recited in the claims. Although the Examiner contends that the use of selectable markers disclosed on page 5 of Rowlands amounts to "permitting expression of said plurality of intracellular immunoglobulin molecules or fragments thereof, under conditions wherein said modified phenotype can be detected," Applicants respectfully disagree with this contention. The use of selectable markers disclosed on page 5 of Rowlands was to indicate whether or not a cell had been infected with vaccinia virus. It does not describe the detection of a modified phenotype in a host cell to determine if an intracellular immunoglobulin molecule or fragment thereof has been formed. Applicants therefore respectfully maintain that Rowlands does not teach or suggest all of the elements of the claimed invention for which the Examiner is relying on it. As such, the Examiner's arguments that Zauderer, and Waterhouse teach the limitations "that are deficient in Rowlands et al." must also fail. *Compare* present Office Action at page 10, and Applicants' remarks, *infra*.

Applicants also note that, in maintaining the rejection under 35 U.S.C. § 103, the other arguments made by the Examiner in the present Office Action are essentially repeated from the Office Action dated January, 27, 2005. In response, Applicants reiterate and maintain their responses as set forth in the Reply filed July 21, 2005, which is incorporated herein by reference in its entirety. In the present Office Action, the Examiner also addressed the Applicants' arguments as presented in the Reply filed on July 21, 2005, to which Applicants provide the following reply and remarks in the same order as set forth in the present Office Action:

Item [1]

See present Office Action at pages 10 and 12. As support for his disagreement with Applicants that the cited references do not teach or suggest the introduction of two expression libraries into eukaryotic host cells, the Examiner asserts that: "Applicants have already acknowledged that the combined references teach the use of two libraries," citing to Applicants' previous Reply dated July 21, 2005. Present Office Action at page 12. However, Applicants believe that the Reply filed July 21, 2005, has been mischaracterized in the present Office Action.

In the previous Reply, Applicants stated that Waterhouse (not the combined references) discloses the introduction of bacteriophage vectors encoding immunoglobulin heavy and light chain variable region fragments that can undergo Cre-*lox* regulated site-specific recombination into bacterial, i.e., prokaryotic, host cells, and suggests that this prokaryotic system can be used to generate large combinatorial libraries by providing repertoires of heavy and light chain fragments. From this, the Examiner seems to have mistakenly drawn the conclusion that Applicants have acknowledged that the references teach or suggest the introduction of two expression libraries into eukaryotic host cells, a conclusion with which the Applicants respectfully but wholeheartedly disagree. Applicants respectfully maintain and emphasize that the cited references do not teach or suggest the introduction of two expression libraries (or even a single expression library, for that matter) into eukaryotic host cells for selecting polynucleotides which encode an intracellular immunoglobulin molecule or fragment thereof that, when expressed, induces a modified phenotype by binding an intracellular

antigen, as in the present invention, nor have they acknowledged at any time that the cited references, either combined or individually, provide such a teaching.

Item [2]

In the present Office Action, the Examiner maintains that one of ordinary skill in the art would have been motivated to combine Rowlands, Zauderer, and Waterhouse. *See* present Office Action at pages 13 and 16. In particular, the Examiner asserts that:

> ...one of ordinary skill in the art would have been motivated to make libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the [sic] their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al.

Id. at 16. The Examiner further asserts that "Waterhouse et al. teach that 'associated' light and heavy chains are a 'preferred' embodiment for screening and/or affinity maturation because they can be 'simultaneously co-selected'. . .which would encompass the 'associated' heavy/light chains described by Rowlands et al." *Id.* at 13 (internal citations omitted). Applicants respectfully disagree with these assertions.

Although both Rowlands and Zauderer disclose the use of vaccinia virus expression vectors in eukaryotic cells, Applicants respectfully submit that there is no motivation or suggestion for one of ordinary skill in the art to combine these references to introduce two expression libraries (or even one, for that matter) encoding immunoglobulin subunit polypeptides into eukaryotic cells for selecting polynucleotides which encode an intracellular immunoglobulin molecule or fragment thereof that, when expressed, induces a modified phenotype in a eukaryotic cell by binding an intracellular

antigen, as recited in the present claims. Rowlands discloses the expression of a previously selected antibody (*i.e.*, not separate, randomly introduced libraries of immunoglobulin light and heavy chains), and Zauderer discloses the introduction of a single expression library into eukaryotic host cells for expressing tumor, cancer, or infected cell-specific antigens. Neither Zauderer or Rowlands discloses the selection of polynucleotides encoding an intracellular immunoglobulin or fragment thereof that, when expressed, induces a modified phenotype in a eukaryotic cell by binding an intracellular antigen.

Furthermore, the "associated heavy and light chains" in Rowlands are not the same as the "associated heavy and light chains" that can be "simultaneously co-selected" in Waterhouse, as suggested by the Examiner, *see* present Office Action at page 16, and both types of "associated heavy and light chains" as disclosed in Rowlands and Waterhouse are different from the present invention. As set forth in Applicants' Reply filed July 21, 2005, Rowlands demonstrated the extracellular expression of a single antibody that had already been selected for heavy and light chains that paired correctly and efficiently (*i.e.*, the CDR-grafted Campath-1H antibody). Waterhouse, on the other hand, discloses simultaneous co-selection of antibody heavy and light chain fragments from prokaryotic host cells that have been recombined by site-specific recombination and which are expressed as fusions of the heavy chain region with the phage coat protein. *See* Waterhouse at page 2265, column 1 (emphasis added). This type of co-selection of heavy and light chain fragments as part of the same vector and expressed as a fusion protein on the surface of a phage particle does not teach or suggest that heavy and light chains would associate to form an intracellular immunoglobulin or fragment

thereof, that, when expressed, induces a modified phenotype in a eukaryotic cell by binding an intracellular antigen, as in the present claims. Furthermore, in using a phage display library, the antibody-bearing phage particles are isolated from the bacterial hosts prior to screening for antigen binding. *See e.g.*, Waterhouse, at page 2266, Figure 1 legend ("About 1010 phage fd particles (including recombinant phage) were harvested from the culture supernatant by centrifuging out bacteria. . .") (emphasis added). As such the phage-displayed antibody fragments do not bind antigen intracellularly.

The motivation or suggestion to combine does not come from Rowlands, because Rowlands discloses extracelluar expression of a single, previously selected antibody. The motivation or suggestion does not come from Zauderer, which Zauderer discloses introduction of one eukaryotic expression library into host cells for expressing tumor, cancer, or infected cell-specific antigens. As set forth, *supra*, neither Rowlands nor Zauderer discloses selection of an intracellular immunoglobulin that, when expressed, induces a modified phenotype in a eukaryotic host cell via binding an intracellular antigen.

The Examiner impermissibly is using the Applicants' own claimed invention as a blueprint to select only those features from each reference that the Examiner believes will support a *prima facie* case of obviousness. The Examiner identifies Rowlands as differing from the claimed invention in that "[Rowlands et al.] do not specifically teach the use of a 'library' of first/second polynucleotides." Present Office Action at page 9. The Examiner further states that, "[h]owever, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al." *Id* at 10. In particular, the Examiner asserts that Zauderer discloses "the use of a 'library of polynucleotides in a

vaccinia virus vector using the 'tri-molecular recombination' approach for screening purposes," and that Waterhouse discloses "that a 'library' can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are 'packaged together' i.e., two libraries." *Id.* at pages 5-6 (emphasis in original). The Examiner also states that "Zauderer et al. also discloses modified phenotypes including Applicants' elected 'cell death' species." *Id.*

Although the Examiner asserts that the cited references supply all of the elements of the present invention, a point with which Applicants respectfully disagree for the reasons detailed above, merely pointing to a collection of disjointed elements in a group of references is not sufficient for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. "[R]ejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'" *In re Rouffet*, 149 F.3d 1350, 1375 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998) (quoting *Sensonics, Inc. v. Aerosonic Corp.* 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996). *See also, In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

Furthermore, the law requires considering each of the cited references *as a whole* in establishing a *prima facie* case of obviousness. "'It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full

appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 147, U.S.P.Q. 391, 393 (CCPA 1965)) (underline in original). In the present case, the Examiner relies on Waterhouse "to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process, regardless of how those antibodies are produced." Present Office Action at page 22 (emphasis in original). Applicants respectfully assert that this characterization of, and reliance on, Waterhouse for such a teaching is improper because it fails to consider the reference as a whole. In particular, relying on the disclosure of Waterhouse in such a manner ignores the fact that the methods disclosed in Waterhouse are performed in a *prokaryotic* system. Waterhouse, when properly considered *as a whole--i.e.*, taking into account the fact that the fragments are fused by at least one of the chains to a phage coat protein, that antibody fragment expression is in prokaryotic cells, and that the antigen binding/selection is extracellulary after isolating phage particles from the host cells--would not be considered by one of ordinary skill in the art as a reference disclosing technique that could simply be extrapolated to a eukaryotic cell system for intracellular immunoglobulin expression and selection, even in light of Zauderer, which discloses the introduction of a single vaccinia virus expression library into eukaryotic host cells for expressing tumor, cancer, or infected cell-specific antigens, and Rowlands, which discloses the expression of a single, previously selected antibody from a vaccinia virus expression vector in a eukaryotic cell. None of these references describes selection of polynucleotides encoding an intracellular immunoglobulin in eukaryotic cells which, when expressed, induces a modified

phenotype via binding intracellular antigen, whether by using one or multiple expression libraries.

As further support that one of ordinary skill in the art would not have considered the phage display methods of Waterhouse to be interchangeable with methods performed in a eukaryotic host, Applicants submitted Exhibit A with their Reply filed July 21, 2005 ("Exhibit A"). As discussed in the Reply filed July 21, 2005, Exhibit A is a copy of the Declaration of Dr. Walter Storkus that was filed in co-pending U.S. Application Serial No. 09/987,456 ("the '456 Application"). Although the Declaration was submitted in specifically as part of the response to the Office Action in the '456 application, a copy was submitted in the present case for illustrative purposes. Namely, to show that, since the invention of the '456 application (selection of polynucleotides encoding antigen-specific immunoglobulins or fragments thereof in eukaryotic cells) was not obvious over Rowlands, Zauderer, and Waterhouse, the present invention (a method of selecting polynucleotides encoding intracellular immunoglobulins or fragments thereof) *a fortiori*, would not have been obvious. As Dr. Storkus stated in Exhibit A, methods using prokaryotic expression systems could not be extrapolated to eukaryotic cells because the conditions for assembly of immunoglobulins from light and heavy chains are different in the eukaryotic cytoplasm than in the periplasmic space of a bacterial host, and that "it could not be known what effect this would have on antibody assembly." Exhibit A filed on July 21, 2005, at page 4. Dr. Storkus's statements apply in the present case as well, because the conditions for intracellular formation of an immunoglobulin or fragment thereof whose expression results in a modified phenotype are different from those

required for the expression of a fusion protein on the surface of a phage particle, and one method cannot simply be substituted for the other. *See also,* [Item 3], *infra.*

In view of the discussion above, the Examiner has not shown that the cited references teach every element of the present invention in and has not provided any satisfactory reasons why one of ordinary skill in this art, seeking to select polynucleotides that encode an intracellular immunoglobulin whose expression induces a modified phenotype in eukaryotic host cells via binding to an intracellular antigen, would combine Waterhouse with Rowlands and Zauderer in such a way that the present invention would be rendered obvious.

Applicants also respectfully submit that, contrary to the assertions on Page 17 of the present Office Action (and asserted again at pages 18 and 21), Applicants have not attempted to overcome the rejection under 35 U.S.C. § 103 by attacking the cited references individually. Rather, Applicants have characterized what is and/or what is not disclosed by each of the cited references, and have shown why these references, either combined or individually, do not teach each and every element of the claimed invention and why there is no motivation or suggestion to one of ordinary skill in the art to combine the cited references. Namely, for the reasons discussed above, the combination of cited references does not teach the selection of polynucleotides encoding an *intracellular* immunoglobulin molecule or fragment thereof whose expression results in exhibition of a modified phenotype in the eukaryotic host cell via binding to an intracellular antigen. Even assuming, *arguendo*, that the references did teach each and every element of the claimed invention, (which they do not), Applicants respectfully maintain that, as discussed in detail above and in the sections below, there is no

suggestion or motivation for one of ordinary skill to combine the cited references. As such, the Examiner has not established a *prima facie* case of obviousness and the rejection should be reconsidered and withdrawn.

Item [3]

In alleging that Waterhouse would suggest to one of ordinary skill art to introduce two expression libraries into eukaryotic cells for selecting polynucleotides which encode an intracellular immunoglobulin molecule, the Examiner asserts that:

> A person of skill in the art (most likely a Ph.D.) working in the field of immunology and/or combinatorial chemistry (i.e., for the purpose of producing antibody and/or antibody libraries) would look to all relevant papers for guidance (e.g. papers encompassing phage display, vaccinia virus, etc.) because the problems encountered are not "unique" to any one system. The advantages obtained from producing large "primary" libraries of heavy and light chains (i.e., two libraries) and the advantages associated with being able to co-select these heavy and light chains in order to produce, for example, antibodies with high affinity are just as applicable to mammalian expression systems as they are to phage display. The products in each case (i.e., the antibodies or antibody libraries) would be the same.

Present Office Action at page 17. Applicants respectfully disagree with these assertions.

First, Applicants respectfully submit that the products in each case would not be the same as the Examiner suggests. The methods of the present invention are directed to selecting polynucleotides that encode intracellular immunoglobulins or fragments thereof. None of Rowlands, Zauderer or Waterhouse discloses selection of an intracellular immunoglobulin or fragment thereof whose expression results in exhibition of a modified phenotype by a host cell via binding to an intracellular antigen.

Second, even assuming, *arguendo*, that all of the elements of the claimed invention could be pieced together from the cited references (a point with which the applications disagree), the eukaryotic systems of Zauderer and Rowlands are not simply "interchangeable" with the prokaryotic system disclosed in Waterhouse and extracellular immunoglobulin expression and selection is not simply "interchangeable" with a system for intracellular immunoglobulin expression and selection. The Federal Circuit considered a similar situation in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), where the court held that a patent claiming a sandwich-type immunoassay that used monoclonal antibodies was not obvious in view of prior art references that disclosed sandwich assays using polyclonal antibodies, even in view of references that disclosed monoclonal antibody production and the use of a single monoclonal antibody in a competitive immunoassay. *Id.* at 1380-81. The Federal Circuit concluded that "[f]ocusing on the obviousness of substitutions and differences instead of on the invention as a whole as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness." *Id.* at 1383.

The present case is analogous to *Hybritech* in that, here, the Examiner is focusing on the notion that a prokaryotic expression library system for selecting antibody fragments as disclosed in Waterhouse can simply be substituted by a eukaryotic system for selecting polynucleotides encoding intracellular immunoglobulins or fragments as in the present invention. As established in *Hybritech*, this is an improper analysis for establishing a *prima facie* case of obviousness. The present invention is not rendered

obvious by a combination of references wherein one discloses that a previously selected antibody can be expressed in eukaryotic cells using vaccinia virus vectors (Rowlands), the second discloses that a single library of vaccinia virus vectors can be introduced into eukaryotic cells for expressing tumor, cancer, or infected cell-specific antigens (Zauderer), and the third discloses a prokaryotic antibody selection system using a repertoire of heavy and light chains packaged into a common phage particle (Waterhouse) because the Examiner has not established that one of ordinary skill in the art would have been motivated to combine these references where none of the cited references discloses selection of polynucleotides encoding in intracellular immunoglobulin or fragment thereof, which, upon expression, induces a modified phenotype via binding to an intracellular antigen. In concluding otherwise, the Examiner impermissibly focuses on the obviousness of substitutions and differences instead of the invention as a whole, and uses "the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *See Rouffet*, 49 F.3d at 1375; *see also*, [Item 5], *infra*. Because there would have been no motivation to combine the cited references without using the claimed invention as a guide, there is no *prima facie* case of obviousness.

Item [4]

The Examiner alleges that the Declaration of Dr. Zauderer, submitted as Exhibit B with Applicants' Reply filed July 21, 2005, is "insufficient" to overcome the rejection under 35 U.S.C. § 103. Applicants believe that the Examiner has misunderstood the capacity in which Applicants submitted Exhibit B with the Reply filed on July 21, 2005.

Exhibit B is a copy of the Declaration of Dr. Zauderer and its accompanying exhibits that was filed in co-pending U.S. Application Serial No. 09/987,456 ("the '456 application). As set forth in Applicants' Reply filed July 21, 2005, in the present case, the copy of the Zauderer Declaration was submitted for illustrative purposes, that is, "as further evidence that one of ordinary skill in the art would not have been motivated to combine Rowlands, Zauderer and Waterhouse," because the same references were cited in the '456 application as in the present case. *See, e.g.,* Reply filed July 21, 2005, at page 34. Since a *prima facie* case of obviousness was not established with respect to the invention in the '456 application (*i.e.*, a method of selecting polynucleotides that encode an antigen-specific immunoglobulin or fragment in eukaryotic cells), then *a fortiori*, the same references could not be used to support a *prima facie* case of obviousness in the present case, wherein the claims recite selection of polynucleotides encoding an *intracellular* immunoglobulin molecule or fragment thereof whose expression results in a modified phenotype of the host cell via binding to an intracellular antigen.

Nevertheless, Applicants still respectfully disagree with the Examiner's arguments as they apply to the context of the present invention: *i.e.,* arguments that there is no factual evidence to support the expert's opinion, that the opposing evidence is strong, and that the nature of the matter that Applicants are trying to establish pertains only to legal conclusions that have been set forth in an entirely conclusory manner. *See* present Office Action at page 15. Applicants respectfully submit that, contrary to the Examiner's assertions, the opposing evidence for supporting an obviousness rejection is not strong. Applicants direct the Examiner to Items [1] to [3], *supra*, as well as Item [5], *infra*, wherein Applicants have set forth in detail why a *prima facie* case obviousness has

not been properly made or supported by the Examiner. Dr. Zauderer's Declaration is consistent with the arguments set forth in those sections.

Applicants also respectfully submit that Exhibit B provides more than legal conclusions that "have been set forth in an entirely conclusory manner," as alleged by the Examiner. Rather, Exhibit B provides specific reasons why, in Dr. Zauderer's opinion as an expert in the fields of immunology and cell biology, a person of ordinary skill in the art would not have been motivated to combine Rowlands with Zauderer and Waterhouse to arrive at the present invention, and would not have had a reasonable expectation of success in doing so. Specifically, Dr. Zauderer states that one of ordinary skill in this art would not have been motivated to combine Waterhouse with Rowlands and Zauderer because Waterhouse discloses a method for providing repertoires of antibody light and heavy chain fragments in the context of phage display, *i.e.*, as fusion proteins with phage surface proteins. Exhibit B at pages 6-7. According to Dr. Zauderer, one of ordinary skill in the art would not have considered the features disclosed in Waterhouse as something that could be expanded for use in eukaryotic systems (*i.e.*, prokaryotic and eukaryotic systems would not have been considered as interchangeable substitutes). *See id.* at 7. Dr. Zauderer concluded, based on the fact that the prokaryotic system of Waterhouse could not be expanded into a eukaryotic system, that one of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands, Zauderer, and Waterhouse to arrive at the present invention. *See id.*

With respect to the Examiner's arguments regarding the discussion of a long-felt need in the art, Applicants respectfully submit that such discussion was not specifically made with respect to the present case. While Applicants do not mean to suggest that

there was not a long-felt need in the art for the presently claimed invention, Applicants note that the discussion regarding a long-felt need in the art addressed in the Zauderer Declaration was specific to the co-pending '456 application. Applicants specifically identified in their Reply filed July 21, 2005, the illustrative purpose for which a copy of the Zauderer Declaration from the '456 application was being referenced. Namely, to show that there was no motivation or suggestion for one of ordinary skill in the art to combine Rowlands, Zauderer, or Waterhouse to arrive at the claimed invention. *See* Reply filed July 21, 2005, at page 35. Since Exhibit B was introduced in the present case to further illustrate that there was no motivation to combine the cited references, Applicants respectfully submit that the Examiner's arguments with respect to the insufficiency of the Zauderer Declaration in showing a long-felt need in the art for the present invention were made erroneously. *See* present Office Action at page 20.

Item [5]

The Examiner disagrees with Applicants that one of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of introducing two random expression libraries into eukaryotic host cells. *See* present Office Action at pages 14 and 21. The Examiner asserts that, because "Rowlands et al teach a method for producing antibodies in vaccinia infected 'mammalian' cells, that "the conclusion that a person of skill in the art would know how to express antibody in a 'mammalian' cell is reasonable." *Id.* at 21. The Examiner further asserts that because "Zauderer et al teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed

by Rowlands. . .the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable." *Id.* at 21-22. Applicants respectfully disagree with these assertions.

As explained in detail in Items [2] and [3], *supra*, this analysis fails to consider the invention as a whole, focusing, instead, on the obviousness of differences and substitutions; it is, therefore, an improper analysis for establishing a *prima facie* case of obviousness. The fact that the Examiner is focusing on the obviousness of differences and substitutions instead of considering the invention as a whole is evidenced on page 22 of the present Office Action, which asserts that "the prokaryotic/eukaryotic distinctions to which Applicants refer are not at issue in this case." Applicants respectfully assert that, quite to the contrary, these differences are at the heart of the issue of why one of ordinary skill in the art would not have been motivated to combine Waterhouse with Rowlands and Zauderer, let alone have a reasonable expectation of success if he did combine the cited references. As set forth in Items [2] and [3], *supra*, the Examiner's reliance on Waterhouse "to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced," present Office Action at page 19, is improper because: 1) it fails to consider the reference as a whole (*i.e.*, that it discloses the use of heavy and light chain immunoglobulin repertoires in a *prokaryotic* system); and 2) because it focuses on the obviousness of differences and substitutions between the cited references and the claimed invention (*i.e.*, eukaryotic substituted for prokaryotic and intracellular expression substituted for extracellular expression), rather than considering the claimed invention as a whole.

Even assuming, *arguendo*, that the Examiner could establish a motivation to combine the cited references (with which Applicants disagree), Applicants respectfully maintain that there would have been no reasonable expectation of success in doing so to achieve the claimed invention. A similar consideration was addressed by the Federal Circuit in *In re Vaeck*. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In *Vaeck* the claimed invention was directed to a chimeric gene capable of being expressed in cyanobacteria cells, comprising a promoter region effective for expression of a DNA fragment in Cyanobacterium and at least one DNA fragment from a insecticidally active *Bacillus* bacterial gene. *Id.* The Federal Circuit determined that there was no motivation to combine, and no reasonable expectation of success in combining: 1) a reference that disclosed the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a CAT selectable marker gene; and 2) three secondary references that collectively disclosed the expression of genes encoding certain *Bacillus* insecticidal genes in three different species of bacterial hosts, two of the genus *Bacillus* and *E. coli*. *Id.* The court determined that "[t]he prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill in the art a reasonable expectation of success in doing so. . . . The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." *Id.* at 493

In *Vaeck*, the bacterial and cyanobacterial hosts that were at issue are both members of the prokaryote kingdom. *Id.* at 489. Unlike in *Vaeck*, the eukaryotic host cells in the method of the present invention and the prokaryotic host cells used in the

phage display methods in Waterhouse are not even in the same taxonomic kingdom. Hence, the differences between the cited references and the claimed invention in the present case are even greater than those in *Vaeck*. *A fortiori*, the present invention is not rendered obvious by the cited references. Accordingly, Applicants respectfully maintain that the Examiner has failed to establish a *prima facie* case of obviousness and that the rejection should be withdrawn.

Item [6]

The Examiner alleges that the Declaration of Dr. Storkus, submitted as Exhibit A with Applicants' Reply filed July 21, 2005, is "insufficient" to overcome the rejection under 35 U.S.C. § 103 because "Applicants' arguments are not commensurate in scope with the claims." Present Office Action at page 22 (citations omitted). Applicants respectfully disagree with this allegation.

First, as with the Zauderer Declaration in Item [4], *supra*, Applicants believe that the Examiner has misunderstood the capacity in which Applicants submitted Exhibit A with the Reply filed on July 21, 2005. Exhibit A is a copy of the Declaration of Dr. Walter Storkus and its accompanying exhibits that was filed in the co-pending '456 application. As set forth in Applicants' Reply filed July 21, 2005, in the present case, the copy of the Storkus Declaration was submitted for illustrative purposes; that is, "as further evidence that one of ordinary skill in the art would not have had a reasonable expectation of success in combining the cited references [Rowlands, Zauderer and Waterhouse]," because the same references were cited in the '456 application as in the present case. *See, e.g.,* Reply filed July 21, 2005, at page 34.

Second, Applicants respectfully disagree with the characterization of Exhibit A set forth in the present Office Action. The Examiner asserts that "[t]he claims do not require 'efficient' introduction of 'good' antibodies as Dr. Storkus contends. In fact, Applicants make clear that low efficiency methods that generate poor antibodies are also to be included within the scope of Applicants' claims." *Id.* The Examiner cites Applicants' previous Reply, which was filed July 21, 2005[1], as support for this assertion. *See id.* ("While the Specification does indicate that direct ligation results in a relatively low recombination efficiency and titer. . . it does not say that methods such as direct ligation or modified homologous recombination. . . cannot be used to generate vaccinia virus libraries. . .") (quoting Applicants Reply filed July 21, 2005, at page 23). However, the excerpt from Applicants' Reply of July 21, 2005, is inapposite to the Examiner's argument because it does not address antibody quality. Rather, these excerpts from the Applicants' Reply were made with respect to the efficiency of insertion of heterologous nucleic acid sequences into vectors in methods by which *expression libraries*, **not** antibodies, are generated.

With respect to the assertions on page 23 of the present Office Action that the combined teachings of Rowlands, Zauderer and Waterhouse refute the evidence presented in the Storkus Declaration, Applicants respectfully direct the Examiner's attention to Items [1] to [5], *supra*, which address in detail why a *prima facie* case of obviousness has not been established by the Examiner.

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[1] In the Present Office Action, the Examiner refers to Applicants' Reply filed on December 7, 2004. Since no Reply was filed on December 7, 2004, in the captioned

Item [7]

In Item [7] of the present Office Action, the Examiner asserts that "Applicants argue, that there was a long-felt and unmet need for the technology of the claimed invention. . ." present Office Action at page 15. Applicants respectfully disagree with the Examiner's interpretation. Applicants did not specifically make such an argument in the Reply filed on July 21, 2005, as suggested by the Examiner. Applicants believe that the Examiner is importing this argument from Exhibit B, a copy of the Zauderer Declaration that was filed in the co-pending '456 application. As set forth, *supra*, Applicants believe that the Examiner has misunderstood the capacity in which Applicants submitted Exhibit B. Applicants explained in their Reply filed July 21, 2005, that, in the present case, the copy of the Zauderer Declaration (Exhibit A) was submitted for illustrative purposes; that is, "as further evidence that one of ordinary skill in the art would not have been motivated to combine Rowlands, Zauderer and Waterhouse," because the same references were cited in the '456 application as in the present case. *See, e.g.*, Reply filed July 21, 2005, at page 34; *see also*, Item [4], *supra*. While Applicants do not suggest that there was not a long-felt need in the art for the presently claimed invention, Applicants note that the discussion regarding a long-felt need in the art presented in the Zauderer Declaration was specific to the co-pending '456 application. As stated above, Applicants specifically identified in their Reply filed July 21, 2005, the purpose for which the Zauderer Declaration from the '456 application was being referenced. Therefore, Applicants respectfully submit that the Examiner's arguments in Item [7] were made erroneously with respect to the present invention.

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application, Applicants assume that the Examiner meant to refer to the Reply filed on

Summary

For the reasons set forth in Items [1] to [7], *supra*, Applicants respectfully submit that the rejection of claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands, Zauderer, and Waterhouse has been overcome or otherwise rendered moot because: 1) the cited references fail to each all of the elements of the claimed invention (in particular, they do not teach or suggest selection of polynucleotides encoding an intracellular immunoglobulin or fragment thereof whose expression results in exhibition of a modified phenotype in the host cell); 2) one of ordinary skill in the art would not have been motivated to combine the cited references; and 3) the cited references would not have conveyed to one of ordinary skill in a reasonable expectation of success in achieving the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

The Rejection of Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 over Rowlands, Zauderer, Waterhouse and Marasco is Traversed

Claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-62 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands, Zauderer, Waterhouse, and Marasco (Marasco, W.A. "Intrabodies: turning the humoral immune system outside in for intracellular immunization" *Gene Therapy* 4: 11-15 (1997) (hereinafter "Marasco"). Present Office Action at Pages 26-27. Applicants respectfully traverse this rejection.

In maintaining the rejection under 35 U.S.C. § 103, the arguments made by the Examiner in the present Office Action are essentially repeated from the Office Action dated January, 27, 2005. In response, Applicants reiterate and maintain their responses as set forth in the Reply filed July 21, 2005, which is incorporated herein by reference in its entirety. In the present Office Action, the Examiner also addressed Applicants' arguments as presented in the Reply filed on July 21, 2005, to which Applicants provide the following reply and remarks in the same order as set forth in the present Office Action:

Item [1](a)

The Examiner has reiterated the argument that, "[f]or claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44 and 59-61, Rowlands et al. and Zauderer et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above. . ." Present Office Action at page 27. In asserting his disagreement with Applicants that there would have been no motivation to combine Rowlands and Zauderer, the Examiner asserts that "to the extent that Applicants are simply repeating their previous arguments, those points were adequately addressed in those sections, which are incorporated in their entirety herein by reference." *Id.* at 29. Applicants respectfully submit that Items [1] to [7], *supra*, address in detail that that Rowlands and Zauderer to not teach or suggest every element of the claimed invention, (in particular they do not teach or suggest an intracellular immunoglobulin that, when expressed, induces a modified phenotype via binding to an intracellular antigen), that there was no motivation for one of ordinary skill in the art to combine Rowlands and Zauderer to arrive at the claimed invention, and that there was no reasonable expectation of success in combining Rowlands and Zauderer to arrive at the claimed invention.

Therefore, Applicants incorporate by reference in this section the arguments set forth in Items [1] to [7], *supra*.

Item [2](a)

The Examiner asserts that Applicants have argued against the Marasco reference individually in asserting that one of ordinary skill in the art would not have been motivated to combine Marasco with Rowlands and Zauderer to arrive at the claimed invention, and would not have had a reasonable expectation of success in doing so. See present Office Action at pages 29-30. Applicants respectfully submit that, contrary to the Examiner's assertions, Applicants have not attempted to attack each reference individually. Rather, as set forth in Item [2], above, Applicants have characterized what is and/or what is not disclosed by each of the cited references, and have shown why these references, either combined or individually, do not teach each and every element of the claimed invention and why there is no motivation or suggestion to one of ordinary skill in the art to combine the cited references.

By distilling the combination of Rowlands and Zauderer down to suggest that together they provide the elements of screening libraries and that Marasco provides the element of using intracellularly expressed and/or localized antibodies like the KDEL-tagged sFV, the Examiner is, again, focusing impermissibly on the obviousness and differences and substitutions and using the Applicants' invention itself "as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *In re Rouffet*, 149 F.3d at 1375. *See also*, Item [2], *supra*. This type of analysis is improper in establishing a *prima facie* case of obviousness.

The disclosure in Marasco regarding the effectiveness of specific intrabodies is not sufficient to establish a motivation for one of ordinary skill in the art to combine this reference with Zauderer and Rowlands to arrive at the methods of the present invention. Marasco suggests only the possibility of selecting an antibody from phage display. *See* Marasco at page 11, column 1. (". . .the creation of large human immunoglobulin libraries from naïve individuals has been achieved and when combined with phage display technology, has allowed investigators to bypass in vivo immunization and produce high-affinity human antibodies to human proteins"). Based on Marasco, an antibody first would have to be selected from phage display (i.e., not intracellularly), and then would have to be cloned into a eukaryotic expression vector and tested for use as an intrabody in a eukaryotic host cell. There is no motivation or suggestion to combine a previously known intrabody of Marasco with a selection technique using phage display libraries in such a way that would render the present invention obvious. As set forth in detail, *supra*, phage display screening methods performed in prokaryotic cells and selection techniques performed in eukaryotic cells would not have been considered merely interchangeable by one of ordinary skill in the art at the time of the invention. *See e.g.*, Items [1] to [7], *supra*. Thus, there is no motivation to combine Marasco with Rowlands and Zauderer to arrive a method for selecting polynucleotides encoding an intracellular immunoglobulin or fragment thereof which, when expressed, induces a modified phenotype in a eukaryotic host cell via binding to an intracellular antigen.

Item [3](a)

The Examiner asserts that:

> ...one of ordinary skill in the art would have been motivated to use intracellular expression of antibodies because, for example, they would allow for the down-regulation of growth factor receptors like interleukin-2..., provide for a defense against tumors..., modulate enzyme function..., treat cancer and or other infectious diseases..., inactivate cytosolic oncoproteins..., inhibit virus replication. . ., etc.

Present Office Action at page 30 (internal citations omitted). Applicants respectfully disagree. As set forth in Item [2](a), *supra*, the disclosure in Marasco regarding the effectiveness of previously known intrabodies is not sufficient to establish a motivation to combine this reference with Zauderer and Rowlands. The suggestion that these references would have been combined by one of ordinary skill in the art at the time of the invention requires the impermissible "use [of] hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *See In re Fine*, 837 F.2d at 1075. Specifically, as discussed above, there is no suggestion to combine the previously known intrabodies of Marasco with an antibody selection technique to select previously unknown intracellular immunoglobulins or fragments thereof in eukaryotic cells that, when expressed, induce a modified phenotype in the host cell via binding to an intracellular antigen. Therefore, there is no *prima facie* case of obviousness.

Item [4](a)

With respect to the motivation to combine Marasco with Zauderer and Rowlands, the Examiner asserts that:

> ...the Marasco/Rowlands/Zauderer distinctions to which Applicants refer are not at issue in this case. ... The Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. The Marasco et al. reference is simply being relied upon to show that a person would be

> motivated to produce a library of intracellular antibodies regardless of how those antibodies are produced."

Present Office Action at page 31.

Applicants respectfully disagree with these assertions, and submit that this characterization of, and reliance on, Marasco for such a teaching is improper because, as set forth in Item [3](a), *supra*, it focuses on the differences and substitutions that would be required to achieve the present invention. In particular, relying on the disclosure of Marasco in such a manner ignores the fact that, at most, the methods disclosed in Marasco suggest only prior selection of an antibody in a *prokaryotic* system, *i.e.*, phage display, in which selection is not performed intracellularly, and then cloning the selected antibody into an expression vector to be expressed as an intrabody. However, when properly considered *as a whole*, Marasco would not be considered by one of ordinary skill in the art as a reference disclosing a technique that could simply be extrapolated to a eukaryotic cell system, even in light of Zauderer, which discloses the introduction of a single vaccinia virus expression library into eukaryotic host cells for expressing tumor, cancer, or infected cell-specific antigens, and Rowlands, which discloses the expression of a single, previously selected antibody from a vaccinia virus expression vector in a eukaryotic cell. This is particularly true since neither Rowlands nor Zauderer, individually or combined, discloses the selection of polynucleotides encoding intracellular immunoglobulins whose expression induces a modified phenotype in eukaryotic host cells via binding to an intracellular antigen. Therefore, the Examiner has not properly established a *prima facie* case of obviousness in the present case.

Summary

For the reasons set forth in Items [1](a) to [4](a), *supra*, Applicants respectfully submit that the rejection of claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, 59-61 and 62 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands, Zauderer, and Marasco has been overcome or otherwise rendered moot because: 1) the cited references fail to each all of the elements of the claimed invention (in particular, they do not teach or suggest selection of polynucleotides encoding an intracellular immunoglobulin or fragment thereof whose expression results in exhibition of a modified phenotype in the eukaryotic host cell via binding to an intracellular antigen); 2) one of ordinary skill in the art would not have been motivated to combine the cited references; and 3) the cited references would not have conveyed to one of ordinary skill in a reasonable expectation of success in achieving the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Based on Non-Statutory Obviousness-Type Double Patenting

In the Office Action at pages 31-36, the Examiner maintained the provisional rejection of claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, and 59-62, for alleged obviousness-type double patenting over claims 84-122 and 127-131 of commonly-owned U.S. Patent Application Serial No. 09/984,456 ("the '456 application") and Marasco.

One of ordinary skill in the art would not have had a reasonable expectation of success in combining Marasco with the '456 application to arrive at the present invention. As discussed, supra, Marasco describes previously known intrabodies, not selection of intrabodies from an expression library. At most, Marasco suggests selecting

in advance an antibody using phage display methods, *then* expressing the selected antibody as an intrabody. There would have been no indication to one of ordinary skill in the art that the methods for selecting polynucleotides encoding antigen-specific immunoglobulin in eukaryotic cells as described in the '456 application could be used to select polynucleotides encoding intracellular immunoglobulins whose expression induces a modified phenotype in the host cell as in the present invention based on the disclosure in Marasco of an *individual antibody* that is expressed as an intrabody. The Examiner is improperly focusing on the obviousness of differences and substitutions in making this rejection rather than on the invention as a whole. *See Hybritech*, 802 F.2d at 1383. Without using the present invention as a guide, there would not have been even a motivation for one of ordinary skill in the art to combine Marasco with the disclosure of the '456 application to arrive at the present invention.

Applicants respectfully submit that, the Examiner has merely plucked elements of the present invention from Marasco (*i.e.*, intrabodies) and the co-pending '456 application (*i.e.*, selection of polynucleotides encoding antigen-specific immunoglobulins from expression libraries in eukaryotic cells) without regard to the context of each reference and without providing sufficient evidence of a motivation to combine them. Neither reference teaches or suggests that eukaryotic expression libraries could be used to select *previously unknown* intracellular immunoglobulins or fragments thereof whose expression induces a modified phenotype in a eukaryotic host cell. As with respect to making a *prima facie* case of obviousness under 35 U.S.C. Section 103, it is improper "to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation

of what such reference fairly suggests to one of ordinary skill in the art.'" *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 147, U.S.P.Q. 391, 393 (CCPA 1965)). Reconsideration and withdrawal of the rejection therefore are respectfully requested.

However, if the Examiner is not inclined to withdraw the rejection, then Applicants respectfully request that this rejection be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '456 application. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

In the Office Action at page 30, the Examiner has also maintained the provisional rejected claims 1-20, 22, 24-27, 29-35, 38, 40-41, 44, and 59-62, for alleged obviousness-type double patenting over claims 46-133 of commonly-owned U.S. Patent Application Serial No. 10/465,808 ("the '808 application") and Marasco. The '808 application is a continuation-in-part of the '456 application, and the Examiner has reiterated the same arguments as presented with respect to the '456 Application. Thus, for the same reasons set forth immediately above with respect to the obviousness-type double patenting rejection over Marasco and the '456 application, Applicants respectfully submit that neither Marasco not the '808 application teaches or suggests that eukaryotic expression libraries could be used to select *previously unknown* intracellular immunoglobulins or fragments thereof whose expression induces a modified phenotype in a eukaryotic host cell. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

However, if the Examiner is not inclined to withdraw the rejection, then Applicants respectfully request that this rejection be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '808 application. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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